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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,605	06/03/2005	Hongbing Zhang	08940.0019	7194

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,605	ZHANG ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21, 24, 54-57, 65-72, 75-79, 88-90, 107-108, 110-113, 115, 121-122, 176, 179, 186, 202, 207-208, 212-215, 225, and 238-239* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-21,24,54-57,65-72,75-79,88-90,107,108,110-113,115,121,122,176,179,186,202,207,208,212-215,225,238 and 239.

DETAILED ACTION

Claims 1-21, 24, 54-57, 65-72, 75-79, 88-90, 107-108, 110-113, 115, 121-122, 176, 179, 186, 202, 207-208, 212-215, 225, and 238-239 are pending. Claims 22, 23, 25-53, 58-64, 73-74, 80-87, 91-106, 109, 114, 116-120,123-175, 177-178, 180-185, 187-201, 203-206, 209- 211,216-224, 226-237, 240-241 are canceled.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1, **4-10,** 13-15, **72, 76** 108, 115, drawn to a modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
(a) wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed into each of the cell types;
(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from **secreted proteins**, extracellular domains of transmembrane proteins, and active fragments thereof; and
(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase.

Group II, claim(s) 2, **4-10,** 13-15, **72, 76,** drawn to a modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
(a) wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types;
(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from **single transmembrane proteins,** multi- transmembrane proteins, kinases, proteases,

phosphatases, phosphodiesterases, kinesins, histone deacetylases, hormone receptors, ubiquitin E3 ligases, and active fragments thereof; and
(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase.

Group III, claim(s) 3, **4-10, 16, 72, 76**, drawn to modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
(a) wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types;
(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide that is **an episomal plasmid** maintenance molecule or an active fragment thereof, and
(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase.

Group IV, claim(s) 1, 11-12, drawn to drawn to a modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
(a) wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed into each of the cell types;
(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from **secreted proteins**, extracellular domains of transmembrane proteins, and active fragments thereof; and
(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase, **wherein the first polypeptide is selected from one or more growth factors**, differentiation factors, anti-differentiation factors, colony stimulating factors, cytokines, lymphokines, anti-inflammatory molecules, apoptotic and other anti-cancer molecules, anti-apoptotic molecules, proteins involved in signaling pathways, antibodies, and active fragments thereof.

Group V, claim(s) 3, 16-20, 24 drawn to modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
(a) wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types;
(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide that is **an episomal plasmid** maintenance molecule or an active fragment thereof, and
(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase, wherein the second heterologous nucleic acid molecule encodes a **second polypeptide** selected from single transmembrane proteins, multi-transmembrane proteins,

kinases, proteases, phosphatases, phosphodiesterases, kinesins, histone deacetylases, hormone receptors, and ubiquitin E3 ligases.

Group VI, claim(s) 3, 16-18, 21, 24, drawn to drawn to modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
(a) wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types;
(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide that is **an episomal plasmid** maintenance molecule or an active fragment thereof, and
(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase, wherein the second nucleic acid molecule is **an RNAi molecule**.

Group VII, claim(s) 3, 16-18, 24, drawn to drawn to modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
(a) wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types;
(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide that is **an episomal plasmid** maintenance molecule or an active fragment thereof, and
(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase, wherein the episomal vector **further comprises a promoter that regulates the expression of the second heterologous nucleic acid molecule.**
Group VIII, claim(s) 54, 65-71, 75, 88, 108, drawn to **non-human chimeric animal** developed from a modified blastocyst comprising a blastocyst from a first animal that comprises a modified stem cell from a second animal or a progeny thereof,
wherein the modified stem cell comprises a stem cell that comprises a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types,
wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from secreted proteins, extracellular domains of transmembrane proteins, and active fragments thereof, and wherein the first polypeptide is other than beta-galactosidase and a recombinase, wherein a method of making a chimeric animal comprising the steps of:
(a) obtaining a modified blastocyst;
(b) implanting the modified blastocyst into a pseudopregnant animal; and (c) allowing the blastocyst to develop into a chimeric animal, wherein the modified blastocyst comprises a blastocyst from a first animal that comprises modified stem cell from a second animal, wherein the modified stem cell comprises a stem cell that comprises a plurality of chromosomes and at least a first heterologous nucleic acid molecule,

wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types,
wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from **secreted proteins**, extracellular domains of transmembrane proteins, and active fragments thereof; and wherein the first polypeptide is other than beta-galactosidase and a recombinase.

Group IX, claim(s) 55, 65-71, 75, 89, drawn to a non-human chimeric animal developed from a modified blastocyst comprising a blastocyst from a first animal that comprises a modified stem cell from a second animal or a progeny thereof, wherein the modified stem cell comprises a stem cell that comprises a plurality of chromosomes and at least a first heterologous nucleic acid molecule, wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types, wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from secreted proteins, extracellular domains of transmembrane proteins, and active fragments thereof, and wherein the first polypeptide is other than beta-galactosidase and a recombinase, wherein a method of making a chimeric animal comprising the steps of:
(a) obtaining a modified blastocyst;
(b) implanting the modified blastocyst into a pseudopregnant animal;
and
(c) allowing the blastocyst to develop into a chimeric animal, wherein the modified blastocyst comprises a blastocyst from a first animal that comprises one or more modified stem cells from a second animal, wherein the modified stem cell comprises a stem cell that comprises a plurality of chromosomes and at least a first heterologous nucleic acid molecule, wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types, wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from **single transmembrane proteins,** multi-transmembrane proteins, kinases, proteases, phosphatases, phosphodiesterases, kinesins, histone deacetylases, hormone receptors, ubiquitin E3 ligases, and active fragments thereof, and wherein the first polypeptide is other than beta-galactosidase and a recombinase.

Group X, claim(s) 56, 65-71, 75, 90, drawn to A non-human chimeric animal developed from a modified blastocyst comprising a blastocyst from a first animal that comprises a modified stem cell from a second animal or a progeny thereof,
wherein the modified stem cell comprises a stem cell that comprises a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types,
wherein the first heterologous nucleic acid molecule encodes a first polypeptide that is an episomal plasmid maintenance molecule or an active fragment thereof, and
wherein the first polypeptide is other than beta-galactosidase and a recombinase, wherein A

method of making a chimeric animal comprising the steps of:
(a) obtaining a modified blastocyst;
(b) implanting the modified blastocyst into a pseudopregnant animal; and
(c) allowing the blastocyst to develop into a chimeric animal,
wherein the modified blastocyst comprises a blastocyst from a first animal that comprises one or more modified stem cells from a second animal,
wherein the modified stem cell comprises a plurality of chromosomes and at least a first heterologous nucleic acid molecule, wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types, wherein the first heterologous nucleic acid molecule encodes a first polypeptide that is **an episomal plasmid** maintenance molecule or an active fragment thereof, and wherein the first polypeptide is other than beta-galactosidase and a recombinase.

Group XI, claim(s) 56, 57, drawn to drawn to A non-human chimeric animal developed from a modified blastocyst comprising a blastocyst from a first animal that comprises a modified stem cell from a second animal or a progeny thereof,
wherein the modified stem cell comprises a stem cell that comprises a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed in the plurality of differentiated cell types,
wherein the first heterologous nucleic acid molecule encodes a first polypeptide that is an episomal plasmid maintenance molecule or an active fragment thereof, and
wherein the first polypeptide is other than beta-galactosidase and a recombinase, wherein the modified stem cell **further comprises an episomal vector.**

Group XII, claim(s) 77, drawn to a method of making a modified stem cell, comprising the steps of:
(a) obtaining a stem cell;
(b) obtaining a first heterologous nucleic acid molecule;
(c) targeting the first heterologous nucleic acid molecule for integration into a chromosome of the stem cell; and
(d) selecting a modified stem cell that comprises the first heterologous nucleic acid molecule, wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from secreted proteins, extracellular domains of transmembrane proteins, and active fragments thereof, and wherein the first polypeptide is other than beta-galactosidase and a recombinase.

Group XIII, claim(s) 78, drawn to A method of making a modified stem cell, comprising the steps of:
(a) obtaining a stem cell;
(b) obtaining a first heterologous nucleic acid molecule;

(c) targeting the first heterologous nucleic acid molecule for integration into a chromosome of the stem cell; and
(d) selecting a modified stem cell that comprises the first heterologous nucleic acid molecule, wherein the first heterologous nucleic acid molecule encodes a first polypeptide that is selected from single transmembrane proteins, multi-transmembrane proteins, kinases, proteases, phosphatases, phosphodiesterases, kinesins, histone deacetylases, hormone receptors, ubiquitin E3 ligases, and active fragments thereof, and wherein the first polypeptide is other than beta-galactosidase and a recombinase.

Group XIV, claim(s) 1, 110-113, drawn to a modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,
(a) wherein the modified stem cell can differentiate into a plurality of cell types; the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed into each of the cell types;
(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from **secreted proteins**, extracellular domains of transmembrane proteins, and active fragments thereof; and
(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase, wherein a method for production of a heterologous polypeptide comprising the steps of:
(a) obtaining a modified stem cell of claim 1; and
(b) **allowing the modified stem cell to proliferate whereby, the heterologous polypeptide is produced**.

Group XV, claim(s) 121, drawn to A composition comprising a first modified and at least a second modified stem cell, wherein the first modified stem cell comprises at least a first heterologous nucleic acid molecule that encodes a first polypeptide, and the second modified stem cell comprises at least a second heterologous nucleic acid molecule that encodes a second polypeptide, wherein the first polypeptide encodes a secreted factor and the second polypeptide encodes a receptor, wherein the first nucleic acid integrates at a first locus of a chromosome of the first modified stem cell and the second nucleic acid integrates at a second locus of a chromosome of the second modified stem cell, and wherein the first and second locus are identical.

Group XVI, claim(s) 176, 179, 186, 202, 207, 208, 212, 213, 214, 215, 225, drawn to A chimeric animal stem cell comprising an animal stem cell and at least one first heterologous nucleic acid sequence, wherein the first heterologous nucleic acid sequence encodes a first human polypeptide other than b-galactosidase, wherein the first heterologous nucleic acid sequence is inserted at a first locus of a chromosome of the non animal, and wherein insertion of the first heterologous nucleic acid sequence at the first locus enables expression of the polypeptide in the chimeric stem cell in both a differentiated and undifferentiated state.

Group XVII, claim(s) 238, 239, 242, drawn to a method of determining gene function in vivo comprising the steps of
(a) providing a modified embryonic stem cell, wherein the modified embryonic stem cell comprises an introduced gene, wherein the introduced gene is a silencer and is

present at a particular locus of the modified embryonic stem cell;
(b) introducing the modified embryonic stem cell into a blastocyst to form a modified blastocyst;
(c) implanting the modified blastocyst into an animal to produce a chimeric embryo, fetus or animal that expresses the introduced gene in more than one tissue; and
(d) determining or observing the effect of the introduced gene on the embryo, fetus, or animal.

The inventions listed as Groups I-XVII do not relate to a single general inventive concept under Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking the inventions of Groups I-XVIII is a modified stem cell comprising a plurality of chromosomes and at least a first heterologous nucleic acid molecule,

(a) wherein the modified stem cell can differentiate into a plurality of cell types;

the first heterologous nucleic acid molecule is integrated into a chromosome of the modified stem cell at a first locus whereby, upon differentiation of the modified stem cell, the first heterologous nucleic acid is expressed into each of the cell types;

(b) wherein the first heterologous nucleic acid molecule encodes a first polypeptide selected from **secreted proteins**, extracellular domains of transmembrane proteins, and active fragments thereof; and

(c) wherein the first polypeptide is other than beta-galactosidase and a recombinase. **Ahmed et al,** (Leukemia Research, 22(2): 119-124, 1998) teaches CD34+ stem cells comprising a plurality of chromosomes and at least a first heterologous nucleiccid molecule, (a) wherein alpha interferon is integrated into a chromosome; (b) the first heterologous nucleic acid encodes a secreted protein; (c) wherein the first polypeptide is other than beta-galactosidase and a recombianse (p 119-124). Therefore the instant technical feature of Groups I-XVIII does not make a contribution over the prior art. Furthermore, the claimed

methods of Groups I-X have distinct method steps, produce different products and/or results, which are not coextensive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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